

# Stem Cell Therapy with Retrograde Coronary Perfusion in Acute Myocardial Infarction. A New Technique

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*A new technique of retrograde infusion of stem cells in the coronary sinus is presented in a 63-year-old man with positive familial history of coronary artery disease and previous acute myocardial infarction. The procedure was successful, and, after 48 hours, the patient left the ICU with no complications.*

Adult stem cells removed from the bone marrow have been used for the treatment of ischemia and acute myocardial infarction, improving ventricular function and/or myocardial perfusion and/or reducing the size of the infarction<sup>1-4</sup>.

We present a new technique for retrograde stem cell infusion in the coronary sinus for the treatment of acute myocardial infarction used for the first time in human beings.

Stem cells have been infused according to the 2 following routes: 1) anterograde intracoronary infusion, about which Gior-dano<sup>5</sup> reported that the endothelium of the coronary microcirculation is continuous, constituting a barrier to the passage of macromolecules to the myocardium; that author also reported that another area of possible resistance is the vascular segment between the artery, in which infusion occurs, and the capillary venous segment; 2) the transendocardial route using the NOGA catheter and electromechanical mapping to identify the viable myocardium, where the mononuclear cells are then injected<sup>6</sup>.

We introduce a third route, retrograde coronary perfusion. We demonstrate that, after injection of a solution of cardiogreen dye or contrast medium in the coronary sinus, and, particularly, in a coronary vein whose corresponding artery is obstructed, the flow is easier and greater in the retrograde direction to the capillary area irrigated by that artery (low resistance), and little or nothing passes to the capillary area of the patent normal coronary arteries<sup>7,8</sup>.

Based on these observations, the hemodynamics team initiated the treatment of myocardial infarction with injection of bone marrow stem cells in a retrograde way through the coronary sinus.

## Case Report

The patient is a 63-year-old, obese man with diabetes, hypertension, dyslipidemia, and a positive familial history of coronary artery disease and previous myocardial infarction in the inferior wall 4 years earlier. Twelve days previously, the patient had an acute myocardial infarction in the anterior wall, which evolved for 14 hours. The patient underwent angioplasty and successful stent implantation but began to complain of fatigue on mild effort and nocturnal paroxysmal dyspnea.

The electrocardiogram showed third-degree left bundle-branch block. The echocardiogram showed cavitory enlargement, anterior and inferior akinesia, and an ejection fraction of 24%. Thallium-201 myocardial scintigraphy showed anterior and inferior fibrosis. The cardiac catheterization evidenced a significantly enlarged ventricle due to anterior and inferior akinesia, and apical dyskinesia. On angiography, the ejection fraction was 25%, and the left ventricular Pd2 was 34 mmHg. The right coronary artery showed a diffuse lesion in its proximal segment and distal occlusion. The left main coronary artery had no obstruction, the circumflex artery had parietal irregularities and occluded marginal branches, and was opacified through the homocollaterals. The anterior descending artery was diffusely damaged from the junction of the middle and distal segments onwards. The first medium-caliber diagonal branch had a severe lesion in its origin.

Taking all this into consideration, the patient and his family were presented with the possibility of retrograde bone-marrow stem cell injection through the anterior descending vein to cause myogenesis and angiogenesis. The patient agreed with the procedure proposed, as did the committee on ethics subordinate to the Argentinean government and Health Ministry.

With the patient under general anesthesia, puncture of the iliac crest and bone marrow aspiration were performed.

The upper layer (leukocyte concentrate containing mononuclear cells) was separated from the erythrocytes by centrifugation, and the latter were reinfused into the patient. Then the leukocytic

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layer was processed so that enrichment in mononuclear cells could be obtained by the separation method through a density gradient (FICOL-HYPAQUE). A satisfactory recount volume ( $13 \times 10^6$ ) was obtained. The procedure was performed in a totally aseptic way, and quantification of the positive cells was performed with the CD34+ cell surface marker, correlated with the pluripotentiality and capacity for differentiation of the subpopulation precursor cells.

A large amount of bone marrow blood was extracted aiming at obtaining a sufficient number of stem cells, avoiding the risk of contamination and cell differentiation.

The technique of stem cell transplantation was performed according to the following phases: 1) puncture of the right external jugular vein, followed by placement of an 8F introducer; 2) infusion of 5,000 IU of heparin; 3) catheterization of the coronary sinus with an Amplatz 8 catheter guide; 4) a 0.014 guidewire and 50x20 balloon catheter were introduced and advanced up to the distal segment of the anterior descending coronary vein; 5) a balloon catheter was positioned and inflated up to 8 atm in the middle third of the anterior descending coronary vein, and the guidewire was removed; 6) 40 mL of stem cells were infused at a pressure of 6 atm through the lumen of the balloon catheter for 5 minutes. No adverse effects occurred; 7) the balloon remained inflated up to 15 minutes after the end of the infusion of the stem cells; 8) after balloon deflation, contrast medium was injected. Opacification of the middle and distal segments of the anterior descending coronary vein and its diagonal branches predominated; 9) removal of the balloon catheter and catheter guide. The patient stayed in the ICU for 48 hours with no complications (fig. 1, 2, 3, and 4).

## Discussion

We initiated our studies on coronary retroperfusion through the coronary sinus in 1962 at the service of Gofredo Gensini, MD, in Syracuse, NY. In April 1962, at the 22nd Annual Clinical Meeting of the American College of Chest Physicians, Syracuse, NY, Murad-Netto, Di Giorgi, and Gensini showed the film "Motion picture studies of the coronary venous circulation." That film resulted

from an experimental study with 25 dogs, whose chests were surgically opened. Their anterior descending artery was occluded in its origin, and, at the same time, a double-lumen catheter was positioned in the coronary sinus, with the proximal lumen connected to a balloon and the distal lumen free for injection of the contrast medium or the cardiogreen dye. The balloon was positioned and inflated after the merging of the posterior descending vein, occluding the coronary sinus, and, simultaneously, the anterior descending vein was occluded and the dye was injected through the free lumen of the catheter, showing its predominant distribution to the ischemic area of the occluded anterior descending artery. When the injection was performed in the anterior descending vein, the distribution to the ischemic area was more evident. These findings were filmed with the conventional device of cine coronary angiography.

With the same objective of causing myocardial revascularization, the authors injected  $H_2O_2$  in the coronary sinus, which colored the venous coronary blood red and produced ventricular fibrillation in dogs.

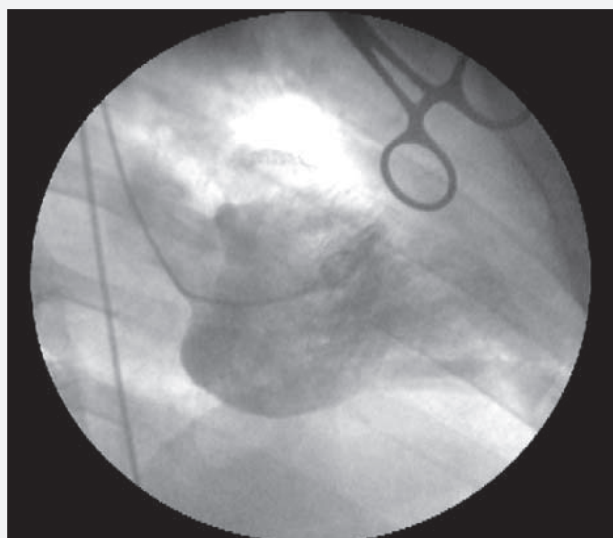


Fig. 2 - Left ventriculogram prior to stem cell transplantation showing severe left ventricular systolic dysfunction.

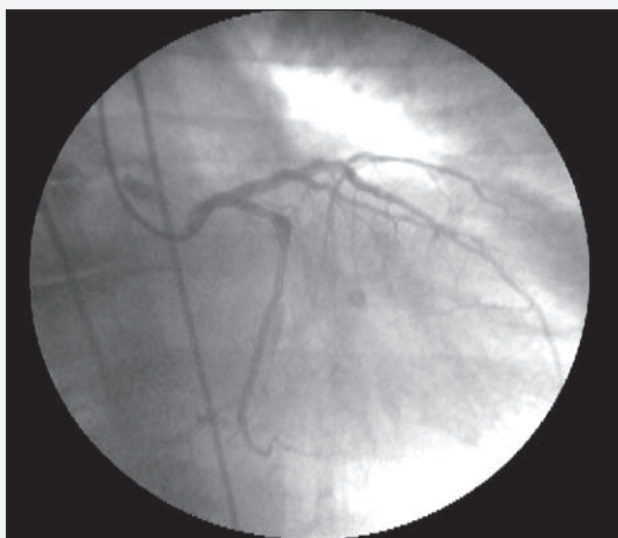


Fig. 1 - Anterior descending arteriogram showing diffuse lesion in the middle and distal segments.

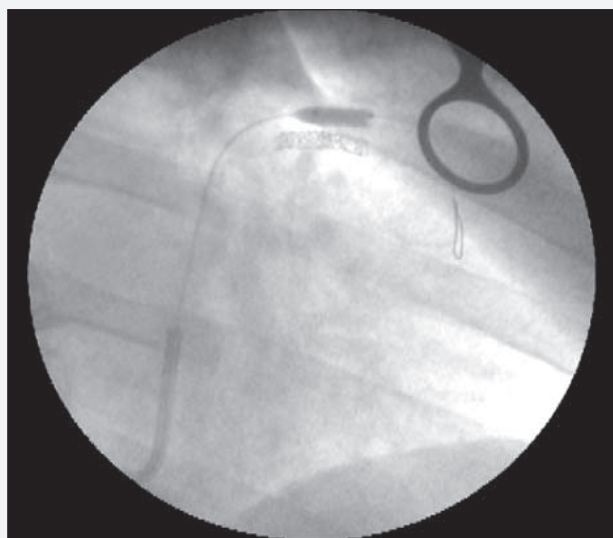


Fig. 3 - Note the guide catheter in the coronary sinus and inflation of the balloon catheter in the anterior descending coronary vein.

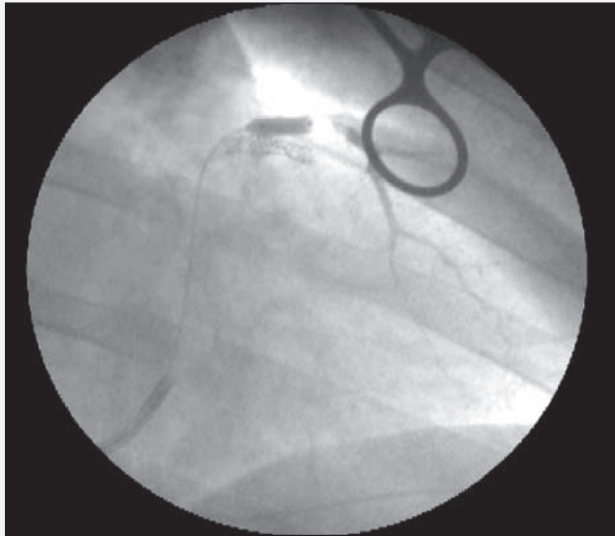


Fig. 4 - Note the contrast medium in the catheter lumen with dominant opacification of the probable ischemic area and also of the occluded right coronary artery.

Gensini et al <sup>7</sup> concluded that the studies about coronary re-troperfusion allowed assessment of the venous coronary circulation and that the technique was innocuous. The easy access to the coronary sinus through catheterization, and, consequently, to the capillaries and myocardium through retrograde injection, also pro-

vided an access route for new methods of diagnosis and therapy with electrolytes and medications. Later on, in May 1962, this same study was presented at the Eleventh Annual Convention of the American College of Cardiology <sup>7</sup>.

In 1973, at the II National Symposium on Atherosclerosis (II Simpósio Nacional sobre Aterosclerose) in São Paulo, Brazil, Murad-Neto<sup>8</sup> reported his experience with 20 patients with different degrees of coronary obstruction, who received injections of contrast medium in the coronary sinus after balloon occlusion. That author<sup>8</sup> showed the predominant distribution of the contrast medium to the areas with a significant coronary obstruction and that the opacification was even more evident when the inferior vena cava was also simultaneously occluded. No complication was observed in any of the cases studied.

We began to use the retrograde route through the coronary sinus for administration of stem cells in the service of Fernandez Viña, MD, in Argentina. To date, we have used this technique of stem cell transplantation in 2 patients with acute myocardial infarction.

In conclusion, the therapy of stem cell infusion for the treatment of acute myocardial infarction via retrograde perfusion of the coronary vein is viable. It provides the possibility that the coronary venous system, easily accessible through right catheterization, can be an entrance route for the treatment of the ischemic myocardium and for other diagnostic and therapeutic purposes, aiming at medicamentous administration to the myocardial tissue.

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